Remarks

This paper is responsive to the Office Action mailed November 5, 2004, setting an initial due date of February 5, 2005. Inasmuch as this paper is filed on or before the initial due date, no fee is due for its consideration.

Objections - Specification

The Office objects to paragraph [053] of the disclosure for the description of amino acids A, V, L, I, P, F, and M as being "polar or hydrophobic." In response to the Office's objection, Applicants have amended paragraph [053] to refer to those amino acids as "***non***polar or hydrophobic." This amendment corrects an obvious clerical mistake and no new matter is added.

The Office objects to paragraph [067] for the alleged recitation of "Figur." Applicants are unable to find the misspelling to which the Office refers. Thus, in response, Applicants submit that paragraph [067] is not objectionable.

Applicants also take this opportunity to correct the recitation of "H47F" in numerous places in the application. As the Office has pointed out, position 47 is glycine, not histidine. Thus, the specification has been amended to recite G47F. Applicants respectfully submit that this is an obvious clerical error and that the amendment adds no new matter.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

The Office rejects claims 1-18 and 22-26 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In response, Applicants respectfully submit that the rejected claims are fully described by the specification.

Initially, Applicants note that the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied where a specification conveys that the inventor had possession of the

invention at the time of filing. The claimed subject matter need not be described literally, or *in ipsis verbis*, in order for the specification to satisfy the description requirement.

Applicants have provided written description support for the claims at several levels of specificity. At the top level, Applicants have pointed out in numerous places in the specification that the mutations are targeted at three main sequences: i) amino acids 41-57, ii) amino acids 94-110, and iii) amino acids 160-173. Next, Applicants have described the different types of mutations that can be made: a) deletions, b) replacements, and c) insertions.

Next, Applicants have elaborated on specific deletions (in paragraph [0112]): any combination of amino acids 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, and 173. Examples of mutations of multiple amino acids include deletion of residues 41-57, 94-110, and/or 160-173. Other examples include deletion of 41-49 or 50-57. Other examples include, but are not limited to, 41-42, 41-43, 41-44, 41-45, 41-46, 41-47, 41-48, 41-50, 41-51, 41-52, 41-53, 41-54, 41-55, and 41-56.

Applicants also elaborated on replacements. Paragraph [0105] describes how nonpolar/hydrophobic amino acids, such as A, V, L, I, P, F, W, and M, can be replaced with polar/acidic amino acids, such as D and E. Paragraph [0106] describes how uncharged/polar amino acids, such as G, S, T, C, Y, N, and Q, can be replaced with polar/acidic amino acids, such as D and E. Paragraph [0107] describes how polar/basic amino acids, such as K, R, and H, can be replaced with polar/acidic amino acids, such as D and E. Paragraph [0110] describes how uncharged/polar amino acids, such as G, S, T, C, Y, N, and Q, can be replaced with nonpolar/hydrophobic amino acids, such as A, V, L, I, P, F, W, and M. Paragraph [0111]

describes how polar/basic amino acids, such as K, R, and H, can be replaced with nonpolar/hydrophobic amino acids, such as A, V, L, I, P, F, W, and M.

There is no requirement that working examples be provided, but Applicants note that a number of specific mutations were made. In particular, reference is made to the following exemplified mutations: deletions of F50 and amino acids 41-52; replacements F44E, T45E, H46A, H46E, G47F, R48A, R48E, G49F, F50E, I51E, T52E, K53E, A54E, I55E, N56E, S57E, L93E, L95E, L96E, L97E, L98E, L99E, V102E, Y160E, L163A, L163F, L163E, Y164E, L165E, L171E, L172E, and H173E.

Thus, Applicants have very clearly described the invention in such terms as to convey to one of ordinary skill that they were in possession of the invention at the time of filing.

Applicants will now briefly address the Office's specific points. The Office states that the specification discloses a Δ41-52 human prolactin molecule (referring to Example 9), but asserts that the specification "does not address any of the other residues that can be subjected to a deletion mutation." (Office Action, page 3, lines 9-10.) Applicants respectfully disagree and point to paragraph [0112], for example, which is discussed above.

The Office states that the specification refers to insertion mutations at pages 19 and 34, and argues that this is the only reference to insertion mutations. The Office proceeds to allege that "Applicants do no [sic] disclose anywhere that they have created a modified human prolactin molecule with an insertion mutation capable of antagonistic activity." (Office Action, page 3, lines 15-17.) Applicants respectfully point out that the claims do not require antagonist activity. Thus, the Office's suggestion that Applicants have failed to disclose an insertion mutation capable of antagonist activity is irrelevant to the written description issue.

Finally, the Office asserts that claims 22-26 are also not sufficiently described. However, there is no explanation as to why these claims, which ultimately depend from claim 1, are deemed as insufficiently described. Applicants assume the rejection flows from the rejection of claim 1, which was also deemed as not sufficiently described. Given that the Patent Office has the initial burden of showing that a claimed invention is not sufficiently described, Applicants respectfully request the Office provide a more detailed rejection if the rejection of claims 22-26 is maintained.

For at least these reasons, Applicants respectfully request the Office withdraw the rejection under 35 U.S.C. § 112, first paragraph, for lack of written description.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Office rejects claims 11, 12, and 19, under 35 U.S.C. § 112, second paragraph, as being indefinite. In response, Applicants have amended the claims to correct the alleged indefiniteness. In all of the claims, chemical descriptors such as "polar," "nonpolar," "acidic," and "basic," have been removed because they were simply descriptive, and thus redundant, of other elements of the claim. Claim 12 has been amended to remove the reference to H47F, because as the Office has pointed out, position 47 is glycine, not histidine. In fact, what was intended was G47F, and claim 10 has been amended to include that mutant. Claim 19 has been amended to remove reference to "greatly," which the Office finds objectionable.

For at least these reasons, Applicants respectfully request the Office withdraw the rejection under 35 U.S.C. § 112, second paragraph, for indefiniteness.

Claim Rejections – 35 U.S.C. § 102

The Office rejects claims 1, 2, 9, and 11 under 35 U.S.C. § 102(b) as being anticipated by Kinet et al. (J. Biol. Chem. 271(24): 14353-14360). In response, Applicants have amended claim

1 to recite that the mutations to region iii) (which encompasses Y169 and H173) are limited to replacements of A, V, L, I, P, F, W, M, G, S, T, C, Y, N, Q, K, R, or H with D or E, or deletions or insertions. Support for this amendment is found, for example, at paragraphs [0105], [0106], and [0107]. Applicants respectfully request withdrawal of the rejection over Kinet et al.

The Office also rejects claims 19-21 under 35 U.S.C. § 102(b) as being anticipated by Goffin et al. (J. Biol. Chem. 269(61): 32598-32608). In response, Applicants have amended claim 19 to clarify that mutations are made to regions i), ii), and iii). The only mutant that Goffin et al. made that exhibited antagonistic activity coupled with less than 1% of native prolacin's agonist activity was A22W, which has a mutation falling outside Applicants' identified regions. Applicants respectfully request withdrawal of the rejection over Goffin et al.

The Office also rejects claims 1, 13, and 14 under 35 U.S.C. § 102(e) as being anticipated by Chen et al. (U.S. Application Publication No. 2004/0127407A1). The Office asserts that Chen et al. teach a deletion mutation at G49. Applicants respectfully disagree.

Chen et al.'s disclosure is directed to, among other things, G129R fusion proteins. G129R is a prolactin molecule that includes a replacement of glycine 129 for arginine, and it is believed to have anti-tumor activities. Chen et al. coupled G129R to other proteins that were believed to impart additional anti-tumor qualities. (See paragraph [0036] of Chen et al. for Chen et al.'s description of the proposed mechanism of action.) G129R is a well-characterized compound, having only one mutation: arginine for glycine replacement at position 129. Chen et al. make no reference to any other mutations in G129R.

Chen et al. correctly recite the sequence of G129R in several places in the application. For example, Figure 1B shows the sequence of G129R, which includes G49; Figure 1F shows a G129R fusion protein with endostatin, which also includes G49. Without explanation, however,

Chen et al. delete G49 in the G129R sequence set forth in Figures 11A and 11B. Applicants respectfully submit that the absence of a G49 in Figures 11A and 11B is a typographical error. The error is repeated in the Sequence Listing. Because of this typographical error, Applicants submit that Chen et al. cannot be considered to place the public in possession of G129 with a G49 deletion, and thus, it cannot be considered a valid reference under 35 U.S.C. § 102(e).

Applicants respectfully submit that the C.C.P.A. case of *In re Harry Louis Yale*, 434 F.2d 666, 168 U.S.P.Q. 46 (1970), is controlling in this instance. In the *Yale* case, the Patent Office had cited art, "Clements," against a patent application that listed a particular chemical compound. The Board affirmed the rejection on the basis that even an erroneous listing would inform one of ordinary skill in the art and would constitute a patent-barring disclosure. The C.C.P.A. reversed the Board's decision, holding that the reference was invalid because the listing it contained was an obvious typographical error, and that it would not describe or suggest the compound to anyone of ordinary skill. "Since the listing of [the compound] in Clements is an error obvious to one of ordinary skill in the art, it cannot be said to describe or suggest the compound to those in the art. The public is not put in possession of the compound." 434 F.2d at 669. (A copy of *In re Harry Louis Yale* is attached for the Office's convenience.) Similarly, because of the mere typographical error, Chen et al. does not place the public in possession of G129R with a G49 deletion.

For at least these reasons, Applicants respectfully request withdrawal of the rejection over Chen et al.

Claim Rejections – 35 U.S.C. § 103

The Office rejects claims 23 and 24 under 35 U.S.C. § 103(a) as being unpatentable over Kinet et al. in view of Fuh et al. (J. Biol. Chem. 270(22): 13133-13137). Applicants respectfully

submit that these claims are not obvious. For the reasons set forth above, claim 1 is neither anticipated nor obvious. Claims 23 and 24 depend ultimately from claim 1 and are patentable for at least the same reasons as claim 1.

For at least these reasons, Applicants respectfully request withdrawal of the rejections for obviousness.

Miscellaneous

Applicants note the reference by the Office to "Shiu, 1985; Manni et al., 1986; Biswas et al., 1987" at page 8, lines 4-5 of the Office Action. It is unclear exactly what documents the Office has considered and referred to in this instance. Applicants respectfully request that the Office show the full citation and indicate that those documents were considered by listing them on a Form PTO-892 in the next official communication.

Conclusion

Applicants respectfully submit that the amendments and remarks herein have placed the application in condition for allowance. If there is any fee due in connection with the filing of this Response, please charge the fee to our Deposit Account No. 03-0172.

Respectfully submitted,

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